REMARKS

Status of claims

Claims 1-6, 8, 10-13 and 32-42 are pending.

Claims 1-6, 8, 10-13 and 32-42 have been rejected.

By way of this amendment, claims 2, 32, 35, 36 are canceled and claims 1, 8, 10-13 and 37-42 are amended.

Upon entry of this amendment, claims 1, 3-6, 8, 10-13, 33, 34 and 37-42 will be pending.

The Official Action indicates that claims 34-42, not claims 32-42, are pending. However, the Official Action notes on page 2, first paragraph that claims 32-42 were submitted and several specific rejections refer to claims 32-42. It appears that the reference to Official Action contains a typographical error in reference to only claims 1-6, 8, 10-13 and 34-42 being pending. Applicants respectfully bring this error to the Patent Office's attention and respectfully note that, in fact, claims 1-6, 8, 10-13 and 32-42 are pending.

Summary of the Amendment

Claims 2, 32, 35 and 36 have been canceled as their subject matter is now contained in other claims.

Claims 1,8, 13 and 32 have been amended to more clearly set forth that the ligand is CD28 or a portion thereof including the extracellular portion. Support for the amendment is found throughout the specification such as on pages 23 and 24. No new matter is added.

Claims 1, 10, 12 and 41 have been amended to recite that the cells to which the compound is delivered is a cell that expresses CD80 and/or CD86. Support for the amendment is found throughout the specification such as on pages 24 and 25. No new matter is added.

Claims 1 and 12 have been amended to recite that the compound is a nucleic acid molecule. Support for the amendment is found throughout the specification such as on page 8 and claim 2. No new matter is added.

Claims 11 and 42 have been amended to more clearly describe a protein complex according to the description in the specification. Support for the amendment is found throughout the specification such as on page 23. No new matter has been added.

Claims 37-42 have been amended to be dependent on claim 34. Support for the amendment is found throughout the specification. No new matter has been added.

Claim Objections

The Detailed Action of the Official Action indicates that claims 1, 11, 12 and 42 are objected to because the claims contain non-elected subject matter. The objection is directed at the term "protein complexes" which the Examiner indicates may refer to protein-protein as well as protein-nucleic acid complexes. Applicants respectfully urge that the term is clearly defined on page 23 of the specification as referring to a complex of two or more proteins that comprise the compound to be delivered. In order to avoid confusion, Applicants have amended claims 11 and 42 to recite the definition in the claim, thereby obviating the rejection.

Claim Rejections under 35 USC 112, first paragraph

Claims 1-6 and 8-13 stand rejected and claims 32-42 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is alleged to as not being described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree.

First it is pointed out that the Official Action states in the paragraph bridging pages 3 and 4 that "The rejection is based on the evaluation of the knowledge of the skilled artisan in the art and the breadth of the claims, which encompass the use of a fusion costimulatory ligand between any portion of any costimulatory ligand and any

portion of any viral protein in the universe." That paragraph also states: "As indicated previously, the claims broadly embrace any combination of above recited proteins in the universe, the number of such fusion ligands would be uncountable, and the function of the resulting fusion ligand thus would be unpredictable." This is incorrect. As amended earlier, the claims specifically refer to CD28 as the costimulatory ligand. Accordingly, the breadth of the claims at issue is not in fact what is asserted in the Official Action.

The Official Action refers to Hurwitz et al (US 5,741,492) and Capon et al (US 6,103,521) as teaching constructs "somewhat contradictory" to the claimed invention. Applicants respectfully point out that it is true that neither Hurwitz et al (US 5,741,492) nor Capon et al (US 6,103,521) teach or suggest the claimed invention. Those patents do not disclose the claimed invention nor do they suggest it. However, they do not state that the invention will not work either.

In determining whether or not a disclosure is enabled, Applicants refer to In re Marzocchi, 439 F2d. 220, 223, 169 USPQ 367, 369 (CCPA 1971) which states:

> As a matter of Patent Office practice, when a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The mere fact that Hurwitz and Capon teach configurations which are different than those of Applicants is not sufficient reason to doubt the objective truth of Applicant's assertion and thereby support an enablement rejection. Hurwitz and Capon

do not suggest the invention and it can be argued that Applicant's configuration is contrary to their affirmative teachings. However, Hurwitz and Capon are both silent with respect to the Applicants' constructs. To support the enablement rejection, the reference would have to say why the claimed invention would not or might not work – not merely teach an alternative configuration.

In the last paragraph of page 6 of the Official Action, which ends the section that relies on Hurwitz and Capon, the Official Action states: "Furthermore, as it is broadly claimed, the substantially uncountable numbers of costimulatory molecules have distinct chemical structures and biological functions." As noted above, the claims were amended earlier and no recite CD28 as the costimulatory ligand.

Page 7 of the Official Action states: "Claims 1-6 and 8-13 stand rejected and claims 32-42 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is alleged to as not being described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Applicants respectfully disagree

This section of the Official Action refers to Applicants amendment. The Official Action states on page 7 "It is unclear whether CD28 and its fusion proteins could promote the delivery of any nucleic acid." The rejection refers to Guibinga, Hurwitz, Capon, Deonarian, McCluskie, Torres and Nakano. Applicant's respectfully urge that, notwithstanding citation of these references, no valid reasoning has been offered to support the enablement rejection.

Applicants note, however, that the last full paragraph on page 9 of the Official Action states

> The specification fails to provide enablement for the full scope of the claims also because the targeting molecule used in the method is now drawn to CD28, whereas cells targeted are drawn to cells that express any type of

> costimulatory molecules, the specification fails to teach how CD28 could target a nucleic acid molecule to cells expressing any type of costimulatory molecules. the [sic]art of record teaches CD28 is a T cell surface molecule, whereas CD80 and CD86 are ligands for CD28 (Janesway Jr.) expressed constitutive and inducibly by antigen presenting cells, in view of such, the claimed method seems only enabled too target APCs.

Applicants have amended the claims so that the cells referred to therein are limited to those cells that express CD80 and/or CD86. In view of this amendment, Applicants urge that the claims are enabled and the rejection is obviated.

For the record, however, Applicants maintain that none of the cited references provide adequate reasoning to doubt the objective truth of Applicants assertion that the claims are enabled. Hurwitz and Capon are discussed above.

With respect to Guibinga et al., the teachings referred to in the Official Action are not relevant to the claimed invention. Guibinga refers to blocking CD28 signaling pathway in order to prevent immune responses against an adenoviral vector used for gene transfer. Applicants are not suggesting effecting CD28 signaling pathway at all. Nothing in Guibinga even suggests that particles with CD28 portions would not be useful to deliver nucleic acid molecules to cells. The enhancement of delivery of an adenoviral vector nucleic acid referred to in the Official Action refers to a means to reduce immune responses against adenovirus vectors. If the particles of the invention were viral vectors, the claimed invention may in fact benefit as described in Guibinga since the targeting of the CD80 and CD86 with the particles would necessarily block some cellular CD28 interaction with the costimulatory molecules. Guibinga et al. does not support the rejection.

Likewise, Deonarian does not support the rejection but rather supports Applicants' assertion. Deonarian refers to the inefficiency of receptor mediated, targeted gene delivery. That it is inefficient does not mean it is not enabled. Rather, reference to

the inefficiency of receptor mediated, targeted gene delivery indicates that the technology does work but at a less than optimal level. It is not necessary to improve something that works in order to be enabled or patentable. Deonarian supports Applicants' assertion that the invention is enabled.

None of McCluskie et al., Torres et al and Nakano et al. support the rejection. None provide any support to question Applicants' assertion that the claimed invention is enabled. Each is, in fact, completely silent on receptor mediated gene transfer and therefore not particularly relevant to the present case.

The claims are enabled. Applicants respectfully request that the rejection under 35 USC 112, first paragraph be withdrawn.

Claim Rejections under 35 USC 112, second paragraph

Claims 1-6, 8-13,32-42 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted that the term CD28 is used incorrectly.

Applicants respectfully urge that the term as used in the specification and claims is not contrary to its ordinary meaning and certainly consistent with the meaning as set forth on pages 23-24 of the specification. However, in an effort to avoid any confusion and advance the application, Applicants have amended to the claims in order to obviate this rejection.

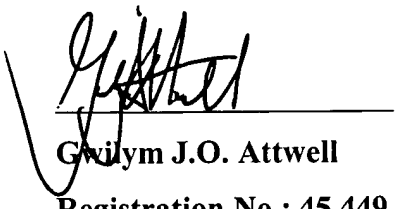
As amended, the claims are clear and definite and in compliance with the requirements of the second paragraph of 35 USC 112. Withdrawal of the rejection is respectfully requested accordingly.

Conclusion

For the foregoing reasons, Applicants respectfully request that claims 1, 3-6, 8,10-13, 33, 34 and 37-42 be allowed. A notice of allowance is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,



Gwilym J.O. Attwell
Registration No.: 45,449

Date: April 21, 2003
Cozen O'Connor
1900 Market Street
Philadelphia PA 19103
(215)665-2000

1. (Twice Amended) A method of introducing a compound into a cell that expresses CD80 and/or CD86 costimulatory molecules, said method comprising contacting the cell with a non-cellular particle that comprises the compound and a [costimulatory] ligand comprising CD28 or a portion thereof including the extracellular region of CD28; wherein said compound is a nucleic acid molecule.

8. (Amended) The method of claim 1 wherein the [costimulatory] ligand is a fusion protein that includes CD28 or a portion thereof including the extracellular region of CD28 [a costimulatory ligand] and a viral portion.

10. (Amended) The method of claim 1 wherein the cell that expresses CD80 and/or CD86 costimulatory molecules is a dendretic cell.

11. (Amended) The method of claim 1 wherein the particle is a viral particle, a [protein] complex that comprises two or more protein molecules and a nucleic acid molecule, a liposome or a cationic amphiphile/DNA complex.

12. (Amended) A method of introducing a compound into a cell that expresses CD80 and/or CD86 costimulatory molecules comprising contacting the cell with a particle that comprises the compound and a fusion protein, the fusion protein comprising the extracellular region of CD28 and the cytoplasmic and transmembrane regions of HIV gp41; wherein said compound is a nucleic acid molecule.

13. (Twice Amended) A method of delivering a therapeutic protein to an individual comprising the step of administering to tissue of said individual at a site on said individual's body, a particle that comprises a nucleic acid molecule that encodes a therapeutic protein and a [costimulatory] ligand comprising CD28 or a portion thereof including the extracellular region of CD28.

32. (Amended) The method of claim 1 wherein the [costimulatory] ligand is a fusion protein that includes CD28 or a portion thereof [a costimulatory ligand] and a viral portion.

37 (Amended) The method of claim 34 [35] wherein the compound is DNA.

38. (Amended) The method of claim 34 [35] wherein the compound is DNA that comprises a nucleotide sequence that encodes a protein operably linked to regulatory elements functional in the cell.

39. (Amended) The method of claim 34 [35] wherein the compound is DNA that comprises a nucleotide sequence that encodes an immunogenic protein operably linked to regulatory elements functional in the cell.

40. (Amended) The method of claim 34 [35] wherein the compound is DNA that comprises a nucleotide sequence that encodes an non-immunogenic protein operable linked to regulatory elements functional in the cell.

41. (Amended) The method of claim 34 [35] wherein the cell that expresses CD80 and/or CD86 costimulatory molecules is a dendretic cell.

42. (Amended) The method of claim 34 [35] wherein the particle is a viral particle, a [protein] complex that comprises two or more protein molecules and a nucleic acid molecule, a liposome or a cationic amphiphile/DNA complex.